DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 6-188/S-018, S-019

Lederle Laboratories
Attention: Salvatore P. Peritore
Associate Director, Regulatory Affairs
401 North Middletown Road
Pearl River, NY 10965-1299

01 OCT 2001

Dear Mr. Peritore:

Please refer to your supplemental new drug applications, S-018, dated December 8, 1998, received December 11, 1998, and, S-019, dated April 3, 2001, and received April 4, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Propylthiouracil Tablets, USP.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert:

For S-018:

DESCRIPTION section

In the sentence of paragraph 3 that begins *"Each tablet contains propylthiouracil 50 mg and the following inactive ingredients,"* the names of all inactive ingredients have been changed to all lower case in place of initial capital letters.

CONTRAINDICATIONS section

The phrase, *"or any of the other product components,"* has been added to the first sentence to read as follows:

> *Propylthiouracil is contraindicated in the presence of hypersensitivity to the drug or any of the other product components and in nursing mothers because the drug is excreted in milk.*

PRECAUTIONS section

The following new section, **Information for Patients**, has been added:

> ***Information for Patients***
>
> *Patients should be advised that if they become pregnant during therapy or intend to become pregnant, they should contact their physician immediately about the desirability of discontinuing the drug. They also should not use propylthiouracil while nursing.*
>
> *Patients should report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. They should report symptoms suggestive of hepatic dysfunction (anorexia, pruritis, right upper quadrant pain, etc).*

Under **Drug Interactions**, this section has been revised to read as follows:

> *Anticoagulants (oral):* The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to propylthiouracil.
>
> *ß-Adrenergic* blocking agents: Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A dose reduction of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.
>
> *Digitalis Glycosides*: Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dosage of digitalis glycosides may be required.
>
> *Theophylline*: Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

The section, "**Usage in Pregnancy,"** has been revised to read, "**Pregnancy."**
In addition, "See **WARNINGS**" has been revised to add a period, "**SEE WARNINGS."**

Under the section, **Nursing Mothers**, the second sentence that reads

> See **WARNINGS**

has been changed to read.

> See **CONTRAINDICATIONS** and **WARNINGS.**

The section, "**Usage in Children"** has been changed to "**Pediatric Use,"**

and the following two sentences have been added to this section:

> *Safety and effectiveness in pediatric patients below the age of 6 have not been established. For pediatric patients 6 years and older, see **DOSAGE AND ADMINISTRATION.***

ADVERSE REACTIONS

The following adverse events have been added:

> vasculitis, glomerulonephritis, and taste perversion.

DOSAGE AND ADMINISTRATION

The subsection "**Adult,"** has been changed to "**Adults."**

The subsection "**Pediatric,"** has been changed to "**Pediatric Patients,"**
and, in the second sentence, "children" has been replaced with "pediatric patients."

After the **HOW SUPPLIED** section, the following change was made.

> *"CAUTION: Federal law prohibits dispensing without prescription."*
>
> has been replaced with
>
> "R_x *only."*

For S-019:

The labeling revisions proposed in S-018 were incorporated into S-019, and S-019 contained six copies of final printed labeling (FPL).

In addition, the following changes from the approved labeling dated June 29, 1990, were noted as follows:

WARNINGS section

> *"ANCA-positive vasculitis"* and *interstitial pneumonitis*" are added to the fourth sentence of the first paragraph, to read as follows:

" . . .The drug should be discontinued in the presence of agranulocytosis, aplastic anemia (pancytopenia), ANCA-positive vasculitis, hepatitis, interstitial pneumonitis, fever or exfoliative dermatitis."

ADVERSE REACTIONS section

The first paragraph is changed to add "exfoliative dermatitis" to the second sentence and to add a third and fourth sentence to read:

". . .Nephritis, glomerulonephritis, interstitial pneumonitis, exfoliative dermatitis, and erythema nodosum have been reported. Reports of a vasculitic syndrome associated with the presence of anti-neutrophilic cytoplasmic antibodies (ANCA) have also been received. Manifestations of ANCA-positive vasculitis may include rapidly progressive glomerulonephritis (crescentic and pauci-immune necrotizing glomerulonephritis) sometimes leading to acute renal failure; fever; pulmonary infiltrates or alveolar hemorrhage; skin ulcers; and leucocytoclastic vasculitis."

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling (FPL) submitted April 3, 2001 (Identifier: CI 4974-4;. Rev. Aug. 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

We note that you have submitted six copies of FPL for S-019. Please submit the copies of final printed labeling (FPL) electronically to S-019 according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 14 additional paper copies of the FPL. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 6-188/S-018 + S-019." Approval of the submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research